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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/498,098	02/04/2000	Jeffrey Stack	AURO1330	8316

7590 07/16/2003

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/498,098	STACK ET AL.	
	Examin r	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,40,50,55,60 and 80-86* is/are pending in the application.

4a) Of the above claim(s) *55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,40,50,60 and 80-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 February 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 5/5/03, as Paper No. 18. The amendment has been entered. Claims 1, 2-4, 23, 38, 50, 55 and 60 have been amended herein. New claims 83-86 have been added. Claims 1-38, 40, 50, 55, 60, and 80-82 are currently pending in the application and are addressed herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Election/Restrictions

3. Claim 55 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim for the reasons of record. Election was made **without** traverse in Paper No. 8.

4. Claims 1-38, 40, 50, 60, and 80-82 are examined herein.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. For instance, see p. 36, line 18 and p. 53, line 6). All embedded hyperlinks must be corrected in response to this Action.

Claim Rejections - 35 USC § 112, second paragraph

6. The rejection of claims under 35 U.S.C. 112, second paragraph, as being indefinite have been withdrawn in light of the amendment to the claims.

Claim Rejections - 35 USC § 112, first paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-38, 40, 50, 60 and 80-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. The instant claims are drawn to methods of detecting an activity in a cell, methods of regulating the concentration of a target molecule in a cell, methods of destabilizing a target protein using chimeric molecules wherein the chimeric molecules comprise a destabilization domain, a linker moiety, and a reporter or target protein. Claims are also drawn to the nucleic acid sequence encoding the chimeric molecule and cells comprising said nucleic acid which express said chimeric molecule.

10. It is noted that the claims are broad and encompass a chimeric molecule wherein the linker domain comprises a recognition motif for an activity (i.e. any activity). Therefore the claims encompass a vast number of activities. According to the specification, the activity can be

a number of different non-enzymatic as well as enzymatic activities capable of covalent and non-covalent modifications. However, the specification appears to indicate that the dissociation of the destabilization domain from the reporter protein (or target protein) is critical for accumulation of the reporter/target protein. Therefore, the linker domain must comprise a recognition motif for an activity which effectively dissociated the destabilization domain from the reporter/target protein. The only activity which has been demonstrated to effectively dissociate the destabilization domain from the reporter/target protein is protease activity. Therefore, the claims encompass molecules for which the specification does not have adequate written description because the claims encompass a linker domain comprising a recognition motif for any activity, but the specification only describes one activity (protease activity) which can effectively dissociate the destabilization domain from the reporter/target protein.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

The specification contemplates a number of enzymatic (such as phosphorylation, meristylation, fucosylation, etc.) and non-enzymatic activities, but none of the activities other than protease activity have been shown to make the peptide cleave required to dissociate the destabilization domain from the reporter/target protein. Therefore, the specification has only

described on species (protease activity) in a genus comprising all possible enzymatic as well as non-enzymatic activities. Furthermore, the prior art does not recognize any activities other than proteases which are capable of making the required peptide cleavage in order for the methods to work. Therefore, the claims are rejected because the specification has not adequately a sufficient number of species encompassed by the claims.

11. Additionally, claims 1-38, 40, 50, 60 and 80-86 are rejected under 35 U.S.C. 112, first paragraph in view of the written description rejection set forth above, and because the specification, while being enabling for certain embodiments encompassed by the claims (see below), does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

12. It is noted that without a sufficient written description describing the species encompassed by the claims, one of skill in the art would not know how to make or use the invention.

13. Additionally, t is noted that the claims encompass methods wherein the methods can be performed in cells in vitro or in vivo and wherein the methods are in vivo, includes in cells of transgenic animals and plants.

14. Wherein the claims are drawn to methods in cells in vitro, (as well as the nucleic acid and host cell comprising the nucleic acid), the claims are enabled only to the extent that the claims read a chimeric molecule wherein the linker domain comprises a protease recognition site.

15. Regarding the claims as they are drawn to methods in cells in vitro, it is pointed out that the claims are broad and encompass a chimeric molecule comprising a destabilization domain, a linker domain and a reporter moiety (or target moiety). The claims indicate that the linker moiety comprises a recognition motif for an activity (i.e. any activity). According to the specification, the activity can be a number of different non-enzymatic as well as enzymatic activities capable of covalent and non-covalent modifications. The enzymatic activities having covalent modifications include: proteolysis, phosphorylation, dephosphorylation, glycosylation, methylation, sulfation, prenylation, and ADP-ribosylation. The activities having non-covalent modifications includes: protein-protein interactions and the binding of allosteric or other modulators or other second messengers such as calcium, or camp or inositol phosphates to a polypeptide (see p. 11, lines 21-27 of the specification). The specification only contemplates molecules comprising a destabilization domain/reporter chimera (see Examples 2-9 and 16) and molecules comprising a destabilization domain/linker domain/reporter chimera (see Examples 10-15); wherein the linker domain comprises a recognition motif for a protease. It is noted that there are no examples indicating the molecules comprise a linker domain wherein the linker domain comprises a recognition motif for any activity other than a protease. For instance, there are no examples demonstrating that the linker moiety can comprise a phosphorylation recognition motif (for testing kinase as well as phosphotase activity) or glycosylation, methylation, sulfation, prenylation, or ADP-ribosylation recognition motifs. Nor are there any

working examples wherein the linker domain comprises a recognition motif for non-enzymatic activities. Considering that the specification appears to indicate that the dissociation of the destabilization domain from the reporter moiety is critical for accumulation of the reporter, the linker domain must comprise a recognition motif for an activity that hydrolyzes peptide bonds in order to dissociate the destabilization domain from the reporter. There are no examples in the prior art that indicate that phosphorylation/dephosphorylation, glycosylation, methylation, sulfation, prenylation, or ADP-ribosylation can result in hydrolysis of peptide bonds. Therefore, the linker domain must comprise a recognition motif for a protease.

16. Wherein the claims are drawn to methods of detecting an activity in cells in vivo, the claims are only enabled to the extent that they read on the methods wherein the reporter protein is a bioluminescent protein; and wherein the linker domain comprises a protease recognition site.

17. Regarding the claims as they are drawn to methods of detecting an activity in cells in vivo, it is pointed out that the claims are broad and encompass a molecule comprising a destabilization domain, a linker domain and a reporter moiety wherein the linker domain comprises a recognition motif for an activity. The activity can be for any of the activities contemplated in the specification. However, the only activity which could dissociate the destabilization domain from the reporter/target moiety is peptide bond cleavage. The only activity which has been shown to cleave peptide bonds is protease activity, as mentioned above. Therefore, the linker domain must comprise a recognition motif for a protease because it is not apparent how any other activity could dissociate the destabilization domain from the reporter protein.

18. Additionally the claims encompass detecting an activity in a cell inv vivo using a chimeric molecule comprising a destabilization domain, a reporter protein and a linker moiety. The specification indicates the reporter protein can be enzymatic moieties (such as alkaline phosphatase, beta-galactosidase, etc), beta-lactamases, bioluminescent proteins, and naturally fluorescent proteins.

19. Wherein the claims are drawn to detecting an activity in a cell in vivo, the only reporter proteins for which the claims are enabled are bioluminescent or naturally fluorescent proteins. In order to detect the activity of the reporter protein in a cell in vivo (i.e., in a living organism) the reporter protein must be able to be visualized in a living cell. Non-bioluminescent and Non-naturally fluorescent proteins cannot be visualized in living cells. Therefore, the claims drawn to detecting an activity in a cell in vivo must be limited such that the reporter protein is a bioluminescent protein or a naturally fluorescent protein.

20. Wherein the claims are drawn to regulating the concentration of a target molecule in cell wherein the cell is in plant or animal (i.e., a transgenic plant or animal which has incorporated the nucleic acids encoding the chimeric molecule into its genome), the claims are not enabled for regulating the concentration of therapeutic molecules in the plant or animal.

21. The claims encompass regulating the concentration of a target protein in a cell in vivo wherein the target protein is a therapeutic molecule in plants (see p. 63-65) or in animals (see p, 53-59). In order for the method to result in the effective regulation of the concentration of the therapeutic molecules, the method must be able to precisely regulate the concentration of the therapeutic molecules in the cells. Without precise regulation of the concentration of the

therapeutic molecules in the cell, the method would not result in any therapeutic effect for the cell. The specification does provide any examples which indicate that the method can be used to precisely regulate the concentration of any molecules in plants or animals. Furthermore, the prior art teaches the challenges of regulating the appropriate level of a molecule of interest in transgenic plants and animals (as mentioned in the previous Office Action). Therefore, without evidence to the contrary, it is highly unlikely that the method could be used to precisely regulate the concentration of therapeutic molecules in plants and animals (including transgenic plants and animals).

Response to Arguments

22. Applicant's arguments filed 5/5/03 have been fully considered but they are not persuasive.

23. Applicants argue that one of skill in the art would be able to make the transgenic animals and plants which properly express the molecules in the plants and animals without undue (routine) experimentation. The Applicants assert that the methods of making transgenic plants and animals are well known and because the specification enables the methods in a host cell, it would only be a matter of routine experimentation in order to make transgenic plants and animals which express the claimed molecules. The Applicants have submitted references in support of their arguments (the references have been considered).

24. In response, the problem with the instant claims is not a matter of simply making the transgenic plants and animals which express the claimed miles, but expressing the molecules at such a particular way that the molecules can regulate the concentration of therapeutic molecules

(as well as target sequences) in the cells of the plants and animals. As mentioned above, to the extent that the claims read on the regulation of therapeutic molecules in a cell, there is no evidence presented that the claimed method would result in the precise regulation of concentration required to result in a therapeutic effect in the transgenic plant or animal. Considering the difficulties recognized in the art with respect to regulating the expression of particular transgenes in transgenic plants and animals, it is highly unlikely (without evidence to the contrary) that the claimed methods could precisely regulate the concentration of the therapeutic molecules.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
July 14, 2003